promoter of] the human cytomegalovirus immediate early region HCMV IE1 promoter and [a] the first intron proximate to the 3' end of the HCMV IE1 promoter.

~~83~~ 18. (Amended) The nucleic acid molecule of claim ~~82~~ 17, wherein the promoter region is [homologous to a promoter region in] derived from a subclone of human cytomegalovirus (Towne strain).

~~87~~ 22. (Amended) A vector for expression of a polypeptide in a mammalian cell, comprising:

a) an upstream origin of replication;

b) a downstream polyadenylation region; and

c) the nucleic acid molecule of claim [81] ~~82~~ 17 interposed between the origin of replication and the polyadenylation region, wherein the enhanced promoter region is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the promoter region.

REMARKS

Introductory Comments:

Claims 60-72 and 73-89 were examined in the Office Action dated April 24, 1996. The claims have been rejected based on: (1) 35 U.S.C. § 112, second paragraph, as indefinite (claims 65 and 81-89); (2) 35 U.S.C. § 112, first paragraph, as nonenabled (claims 60-70, 72 and 74-89); (3) 35 U.S.C. § 102(e) as anticipated (claims 60, 61, 63-70, 76-78 and 81-89); (4) 35 U.S.C. §102(b) as anticipated (claims 60-70, 72 and 74-89) and (5) 35 U.S.C. § 103 as obvious (claims 62, 74 and 75). These rejections are believed to be

overcome in part by the amendments and are otherwise traversed for reasons discussed below.

Applicants note that claims 26, 60-72 and 74-89 were pending in the application when the Office Action issued. However, the Office did not acknowledge the pendency of claim 26 in the Office Action. Clarification is respectfully requested.

Applicants acknowledge with appreciation that the Office has corrected the inventorship in this application pursuant to 37 C.F.R. §1.48. Applicants also note with appreciation the withdrawal of the following: (1) the rejection of claims 60-80 under 35 U.S.C. §112, second paragraph; (2) the rejection of claims 60, 61 and 63-72 under 35 U.S.C. §102(b) over Foecking et al. (1986); (3) the rejection of claim 62 under 35 U.S.C. §103 over Foecking et al.; and (4) the rejection of claims 74 and 75 under 35 U.S.C. §103 over Foecking et al. and van Zonneveld et al. (1986).

The Office has requested that applicants clarify the status of U.S. patent application serial numbers 907,185 and 071,674 that were included with the Information Disclosure Statement filed October 16, 1995. These U.S. applications are the priority documents recited in U.S. Patent No. 5,024,939 to Gorman (cited by the Office against applicants' claims) as well as the priority documents in a related European patent application to Gorman. Copies of the priority documents became available to the public after the publication of the European patent application, i.e., after March 16, 1988. Hence, the Examiner's assumption that "applicants had their respective teachings available to them prior to invention of the instantly claimed subject matter" is incorrect. Applicants' priority date with respect to the

claimed subject matter is at least as early as December 24, 1987.

Overview of the Amendments:

Claims 63-65, 79 and 80 have been cancelled without prejudice and disclaimer, in order to advance prosecution. It is to be understood that cancellation of these claims is not meant to be an acquiescence to any outstanding rejections, and applicants reserve the right to bring the claims again in a subsequent, related application.

Claims 60, 66, 67, 71, 76, 78, 82, 83 and 87 have been amended. In particular, claim 60 has been amended to remove language objected to by the Examiner and to recite that the transcription regulatory region includes the first HCMV IE1 intron. This limitation was previously recited in dependent claim 65 which has been cancelled in this response. Claims 66, 67 and 71 have been amended to remove language objected to by the Examiner.

Claims 76 and 78 have been amended to recite that the transcription regulatory region from HCMV IE1 includes the first HCMV IE1 intron. Support for these amendments can be found, *inter alia*, in Figure 29, and in the specification at, for example, pages 57 and 58.

Claim 82 has been amended to remove language objected to by the Examiner and to recite that the enhanced promoter comprises the HCMV IE1 promoter and the first HCMV IE1 intron. Support for this amendment can also be found in Figure 29, and in the specification at pages 57 and 58.

Claim 83 has been amended to remove language objected to by the Examiner, and claim 87 has been amended to correct an inadvertent typographical error in the recited claim from which claim 87 depends.

Accordingly, no new matter has been added to the application by way of the above amendments.

The Rejections under 35 U.S.C. §112, Second Paragraph:

Claims 65 and 82-89 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite, on the grounds that "they do not clearly establish that the intron proximate to the 3' end of the HCMV IE1 promoter is the first intron of the HCMV IE1 region."

Applicants note that claim 65 has been cancelled by the present amendment, and that the limitations of claim 65 have been added to claim 60. Claims 60 and 82, as now amended, clearly recite that the transcription regulatory region includes the first HCMV IE1 intron. Accordingly, this ground of rejection has been overcome.

The Office also states that the relationship between claims 60, 81 and 87 "is puzzling." Applicant has amended claim 87 to depend from claim 82 instead of claim 81. Accordingly, claims 87 is no longer related to claim 60, and this ground of rejection has been overcome.

For all of the foregoing reasons, applicants submit that the rejection of claims 65 and 82-89 under 35 U.S.C. §112, second paragraph, has been overcome by the amendments to the claims. Reconsideration and withdrawal of the rejection is respectfully requested.

The Rejections under 35 U.S.C. §112, First Paragraph:

Claims 60-70 and 72-89 have been rejected under 35 U.S.C. §112, first paragraph, as nonenabled. The Office asserts that given the subject matter of 63 and 65, "it is clear that the scope of 'transcription regulatory region' as now envisioned is not that of the original specification."

Applicants do not agree with the Examiner's assessment of the enablement provided by the specification. However, claims 63 and 65 have been cancelled by this amendment, rendering this ground of rejection moot.

Claims 79 and 80 have also been rejected under 35 U.S.C. §112, first paragraph, as nonenabled. The Office asserts that applicants' specification fails to provide guidance in the use of the intron *per se*. Applicants respectfully disagree. In Example 2.3.2, at pages 57 and 58 of the specification, applicants describe the components, and the actual construction, of the CMV IE-1 expression vector pCMV6a which includes the first HCMV IE1 intron. Applicants also describe how to use an expression vector containing the subject intron to improve expression of an operatively linked coding region (gp120) in COS and other mammalian cells. A significant increase (e.g., a 50-100 fold increase) in the expression of gp120 polypeptide was obtained using the intron-containing vector when compared to an SV40-based expression system. Accordingly, applicants have indeed provided sufficient guidance regarding how to use the intron.

However, claims 79 and 80 have been cancelled in this response in the interest of advancing prosecution. Thus, the present ground of rejection is moot.

Claims 60-70 and 74-89 have also been rejected under 35 U.S.C. §112, first paragraph, as nonenabled. In particular, the Examiner has objected to the use of the term "homologous" when referring to regions present in HCMV and SV40. Applicants have amended claims 60, 66, 67 and 82 to remove this language. Accordingly, this ground of rejection has been overcome.

For all of the foregoing reasons, the rejections of claims 60-70 and 72-89 under 35 U.S.C. §112, first

paragraph, have been overcome by the amendments. Reconsideration and withdrawal of these rejections is earnestly solicited.

The Rejections under 35 U.S.C. §102:

Claims 60, 61, 63-70, 76-78 and 81-89 have been rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 5,024,939 to Gorman ("Gorman"). The Office argues that Gorman is anticipatory, since at column 17, "the construction of an expression plasmid is described, which comprises the CMV enhancer, promoter and splice donor site, an Ig variable region intron and splice acceptor sequence, and the polyadenylation site and transcription termination site of SV40," and at column 13, "vectors containing an SV40 origin of replication are described." Applicants respectfully disagree.

The plasmid which the Office has cited against applicants' claims (Gorman's pF8CIS) does not contain the first HCMV IE1 intron. However, all of applicants' claims, as now amended, expressly recite the first HCMV IE1 intron. Thus, the rejection of claims 60, 61, 63-70, 76-78 and 81-89 over Gorman has is improper. Reconsideration and withdrawal of the rejection of those claims under 35 U.S.C. §102(e) is thus respectfully requested.

Claims 79 and 80 have been rejected under 35 U.S.C. §102(b) as anticipated by Boshart et al. (1985) and Stenberg et al. (1984). The Office has not communicated the basis for these rejections, and applicants have thus not been given a fair opportunity to respond to these rejections. However, applicants do respectfully disagree. In addition, claims 79 and 80 have been cancelled by this amendment, and the rejections are therefore moot.

Claims 60-70, 72 and 74-89 have again been rejected under 35 U.S.C. §102(b) over Chapman et al. (1991). The Office asserts that "applicants have yet to provide evidence that the broadly claimed invention has written description in the application as originally filed." Applicants respectfully submit that this ground of rejection is improper.

As discussed above, applicants have described the CMV IE-1 expression vector pCMV6a which includes the first HCMV IE1 intron. This description can be found in the specification as filed at pages 57 and 58 and in Figure 29, and is sufficient to support all of applicants pending claims. In addition, the Office has previously acknowledged that a "written description of an expression vector containing the human cytomegalovirus immediate early region (HCMV E1) occurs in SN 07/138,894 with a filing date of **December 24, 1987**." (Paper No. 8, page 4). Applicants note that the present application derives from that application (Serial No. 07/138,894). Further, applicants have claimed, and are entitled to the priority of, the December 24, 1987 filing date of Serial No. 07/138,894 pursuant to 35 U.S.C. §120. Chapman et al., however, published in 1991. Accordingly, the reference is <u>not</u> prior art and therefore is <u>not</u> properly citable against the present claims under 35 U.S.C. § 102(b).

Reconsideration and withdrawal of the rejection of claims 60-70, 72 and 74-89 under 35 U.S.C. § 102(b) is thus respectfully requested.

<u>The Rejections under 35 U.S.C. § 103</u>:

Claim 62 has been rejected under 35 U.S.C. §103 as unpatentable over Gorman. The Office states "the vectors taught by Gorman do not appear to contain the *Sal*I site

recited in claim 62 ... [however] it is well known in the art to insert a plurality of restriction sites into linker regions so as to permit the correct orientation of the inserted sequence." Applicants respectfully submit that this ground of rejection is improper.

Specifically, the Office has failed to provide a *prima facie* showing of obviousness over the combination of Gorman with "a general art recognition" of the use of restriction sites in polylinkers. Gorman fails to teach or suggest an expression vector which contains the first HCMV IE1 intron. As shown in Example 2.3.2 of applicants' specification, expression vectors containing the intron are superior to vectors not containing the intron (i.e., 50 to 100-fold more efficient). Amended claim 60, from which claim 62 depends, expressly recites the inclusion of the first HCMV IE1 intron. Thus, the Office has failed to identify any modification of, or combination with, Gorman which would teach or suggest the expression vector of claim 62.

For all of the foregoing reasons, the rejection of claim 62 under 35 U.S.C. §103 over Gorman is improper. Reconsideration and withdrawal thereof is respectfully requested.

Claims 74 and 75 have been rejected under 35 U.S.C. §103 over the combination of Gorman and van Zonneveld et al. (1986). To support this rejection, the Office merely combines van Zonneveld's description of signal sequences (e.g., the signal sequence of human tissue plasminogen activator) with Gorman's expression vector. Applicants respectfully submit that this rejection is also improper.

Claims 74 and 75 depend, indirectly, from claim 60 which includes the express recitation of the first HCMV IE1 intron. As described above, Gorman fails to teach or suggest an expression vector which contains the first HCMV

IE1 intron. This missing feature is neither taught or suggested by van Zonneveld, and the Office has thus failed to provide a *prima facie* showing of obviousness over the combination. Accordingly, the rejection of claims 74 and 75 under 35 U.S.C. §103 is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Conclusion

Applicants respectfully submit that the claims define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

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